Bandolier 24

What do we think?
What do we know?
What can we prove?

Evidence-based health care

First published February 1996

GENEWATCH

Sex change priest in mercy dash to palace shock!

One of the characteristics of health care that attracts a lot of attention is the time it takes for ideas of proven effectiveness to enter clinical practice. The other side of the coin is the rapid dissemination of interventions of unproven effectiveness - sometimes without formal identification of possible harm. The book review on anti-arrhythmic drugs in ***Bandolier*** 23 is a short but good example of this.

Factor V Leiden

This gene is an important risk factor for thrombosis, involved in perhaps 15% of deep-vein thrombosis in the under-70s and up to 50% of familial thromboses. An important paper in the Lancet [1] has shown that the allele is common in European populations, but virtually unknown in several other populations.

The overall frequency of the allele in European and UK populations is 4.4%, and highest in Greeks at 7%.

The authors of the study emphasised very clearly at the end of their report: "Factor V Leiden is an important risk factor for venous thrombosis. The high prevalence suggests that prospective trials to assess the medical and economic desirability of screening before surgery and pregnancy in Europeans should be undertaken".

Headlines

When a story about the study appeared in Doctor magazine about five days after the Lancet publication, the tone of the message was very different:

"Gene tests point to pill clots peril"

Although not quite in the class of "Sex change priest in mercy dash to palace shock" (always said to be the headline writer's acme), this is still fairly startling and implies that action should be taken.

The story linked the factor V Leiden research to the "pill scare" of October. They properly report the principal author as saying that the advantages of screening need to be offset against the consumption of resources, but with this headline, as opposed to the final sentence of the Lancet paper, they have moved implementation a notch nearer - emphasising particularly that many hospitals can provide this test. We know from colleagues in general practice and family planning that factor V Leiden tests are being offered at £25 a time.

What should be done about this gene? The answer, so far as the clinician or family planning doctor is concerned, is nothing. Testing for factor V Leiden raises an interesting possibility, but until the test has been tested it should not be used. Well conducted studies will provide answers about the appropriate place of testing, and what benefits or harms will accrue.

Reference:

1 DC Rees, M Cox, JB Clegg. World distribution of factor V Leiden. Lancet 1995 346: 1133-34.

HRT AND BREAST CANCER

One of ***Bandolier's*** GP readers has picked up on the thoughtful BMJ editorial by Klim McPherson [1] on the use of hormonal supplements in postmenopausal woman, and their effects on the risk of breast cancer. ***Bandolier*** is not in a position to produce a full risk assessment balancing all the arguments, but is able to lay out some of the issues.

Balance of risk

The thrust of this editorial, and the arguments about the use of HRT are, roughly, these:-

1 A 50 year old woman has a baseline lifetime risk of coronary heart disease of about 45%, of hip fracture of about 15% and of breast cancer about 8%.

2 HRT can suppress menopausal symptoms and prevent osteoporosis.

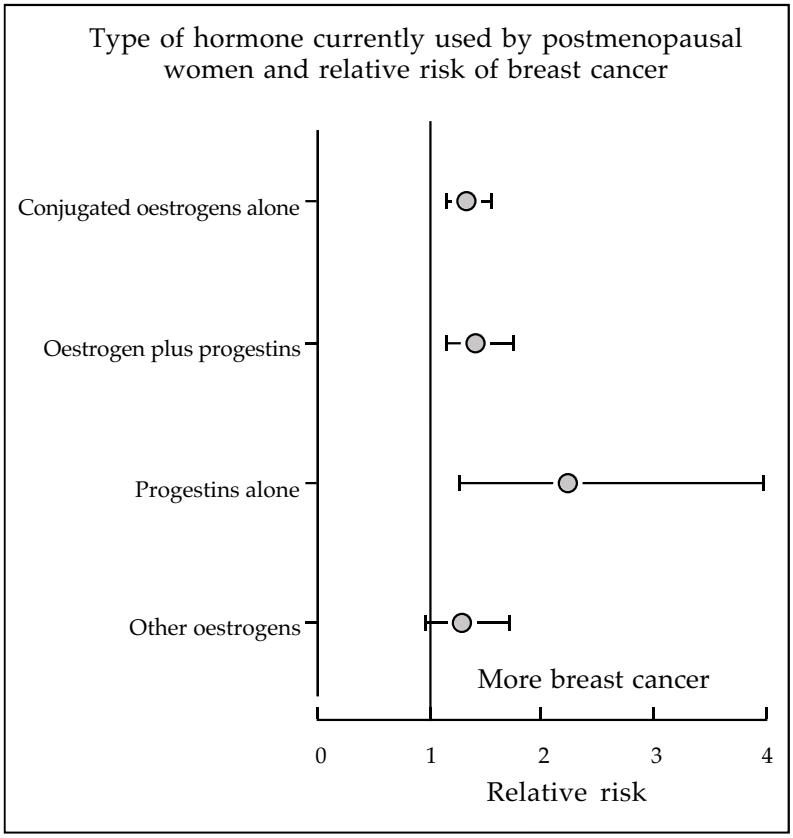
3 HRT may be protective against coronary heart disease.

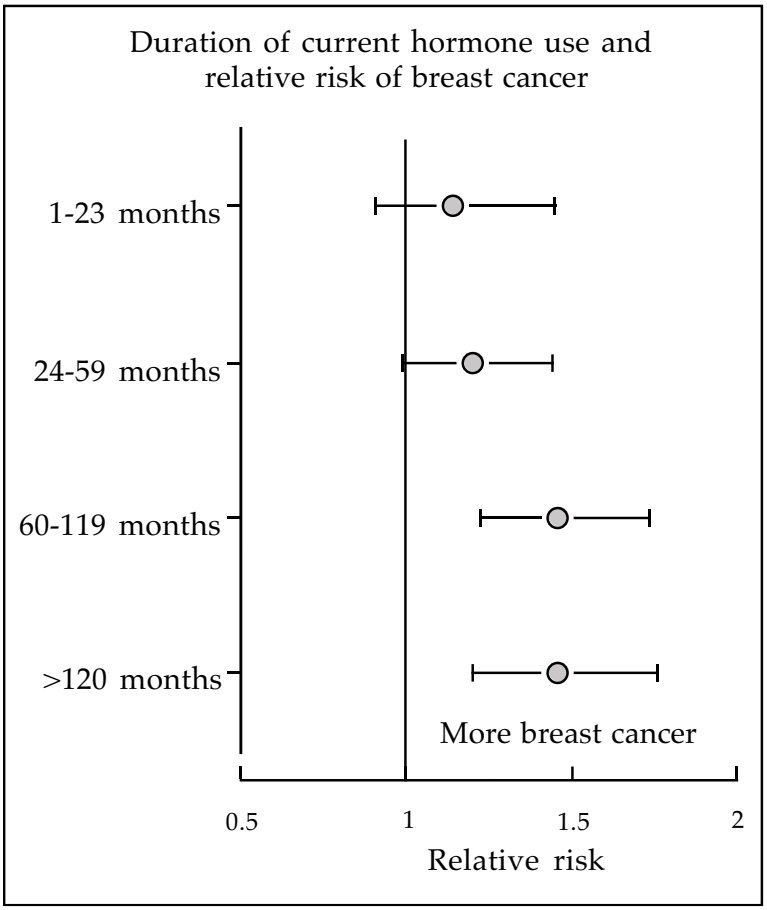
4 HRT may be associated with increased risk of breast cancer.

Clearly there is a balance between likely benefit and harm which may be measured in length and quality of life depending upon how large are the effects of HRT on osteoporosis, heart disease and breast cancer.

Nurses' Health Study

This is a US study involving nearly 122,000 female nurses aged 30 to 55 years in 1976. They have been followed every two years since then, with detailed questionnaire which included items about known or suspected risk factors for cancer and cardiovascular diseases.





Breast cancer diagnosis (or death) was one outcome, and details about newly diagnosed cancers were obtained, with permission, from hospital records and reviewed for over 93% of cases identified. Data from women with carcinoma in situ, who reported breast cancer in 1976, or who were premenopausal were omitted [2].

This left some 24,000 women who were postmenopausal in 1976, rising to nearly 70,000 by 1990. Follow up of index cases was over 95% for breast cancer diagnosis and 98% for fatal breast cancer .

Risk assessment

The relative risk was defined as the incidence of breast cancer among women who had taken hormones after the menopause divided by the incidence in women who had never taken such therapy. Various statistical methods were used to avoid bias from different sources.

Results

There were 725,000 women-years of follow up, with 1935 cases of breast cancer among postmenopausal women.

- Use of any type of hormone or combination increased the risk of breast cancer for conjugated oestrogens alone, for oestrogen plus progestins and for progestins alone.
- For current users of postmenopausal hormones the increased risk of breast cancer became significant when hormones had been used for more than five years.
- Women who had formerly used postmenopausal hormones had no significantly increased risk compared with women who had never used hormones, and this was true even for women who had taken hormones for five or more years in the past.

The magnitudes of the increased risks are shown in the figures. For women currently taking postmenopausal hormones for more than five years, the increased risk of breast cancer was about 50%. A somewhat greater increased risk of about 70% was found with women aged 60-64. The increased risks probably lasted for about two years after women stopped taking the hormones.

What's the answer?

This is a multifaceted problem, and without all the facts it is probably not possible to be definite. McPherson [1] expands on how finely balanced the arguments may be. Crucially important is the length of the protective effect of hormone supplements after administration stops.

Bandolier 3 reviewed the Effective Health Care bulletin on hormones and osteoporosis. ***Bandolier*** 18 examined the genetics of breast cancer , and ***Bandolier*** 20 looked at measures that might reduce falls in the elderly.

Hormones are not the only answer. What we can be sure of is that postmenopausal women using hormone replacement are at relatively little increased danger of breast cancer for the first five years of their use.

What are the other questions?

One of the major issues is osteoporosis, which has been called "a silent epidemic".The burden of osteoporosis to the many, and increasing, numbers of elderly women (and men) is important on a personal basis; the NHS performs some 60,000 operations for hip fractures every year, and there may be 40 premature deaths every day. It may cost the NHS over £700 million a year

Coronary heart disease is the major cause of death in women; prevention may be better than treatment. Its importance was one reason why it was chosen for the second Bando ***lier*** conference. A useful, general, review of prevention of both osteoporosis and coronary heart disease in primary care has recently been published [3] and is a thoughtful, if gentle, way in to these important subjects.

References:

1 K McPherson. Breast cancer and hormonal supplements in postmenopausal women. British Medical Journal 1995 31 1: 699-70.
2 GA Colditz, SE Hankinson, DJ Hunter et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. New England Journal of Medicine 1995 332: 1589-93.
3 C Waine. Prevention of both osteoporosis and coronary heart disease in primary care. British Journal of Clinical Practice 1996 50: 44-6.

Health services research and breast cancer

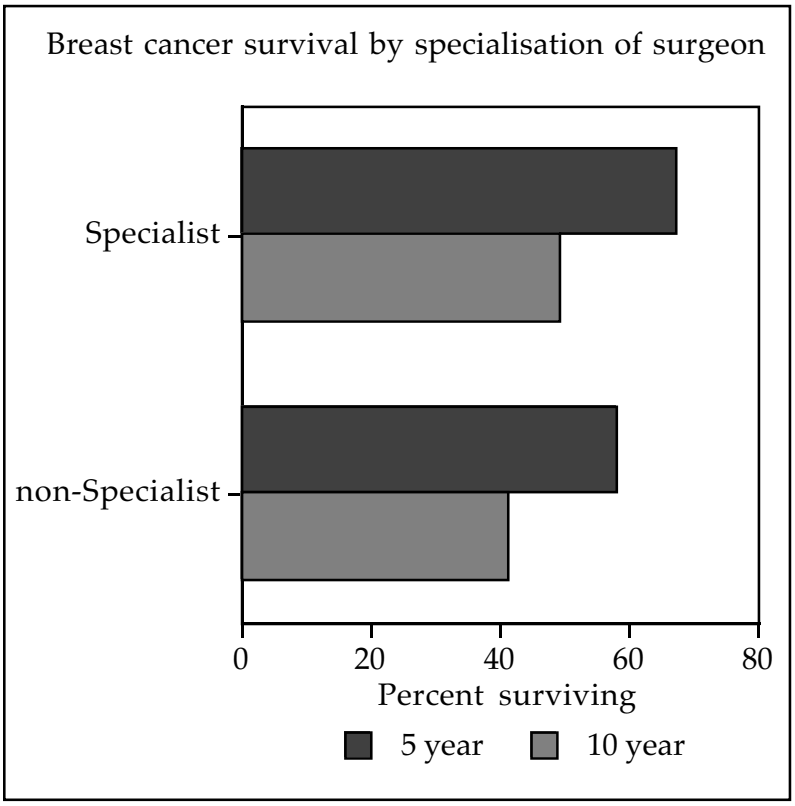
Health services research tends to have an unglamorous image; some people are not even sure what its objectives are, what it does, or whether it provides value for money It is therefore notable that a comment in a recent BMJ is entitled "miraculous developments from health services research" . The piece should be of particular interest to our readers since it concerns breast cancer care.

Specialist centres do better

The comments are based on the findings of a study of survival outcomes of 3786 breast cancer patients treated in the west of Scotland between Jan 1980 and June 1988 and followed to the end of 1993 [1]. The five year survival rate was 9% higher and the 10 year rate 8% higher for patients treated by specialist surgeons compared with those treated by general surgeons (see figure). When appropriate adjustments were made to standardise the results the reduction in the risk of dying looked even better at 16%. The benefits of specialist care were found across all sub-groups examined, such as different ages of patients, different sizes and stages of tumours, and patients from diferent socio-economic backgrounds.

Design

The study was conducted in a defined population of 1.5 million people in the west of Scotland, with 98% of all known cases of histologically verified cases of breast cancer being included during the years 1980-1988. Some 918 patients were treated by surgeons with a special interest in breast cancer , compared with 2868 patients treated by surgeons with no special interest. Most patients (89%) were treated at their local hospital.



For the purposes of this study, surgeons with a special interest in breast cancer were defined as setting up a dedicated breast clinic, a defined association with pathologists and oncologists, organising and facilitating clinical trials and maintaining a separate record of all patients with breast cancer in their care.

Comment

The message is a clear one and confirms what a number of leading oncologists have been saying for some considerable time now, namely that the survival of patients with breast cancer is better when they are treated by surgeons with a special interest in breast cancer rather than by general surgeons. It is a case where, as with hip fractures [2], an overall package of care may prove to be more important than any particular item of the package.

Such significant differences have implications for the provision of services for the treatment of women with breast cancer and almost certainly for patients with many other types of cancer. There is an urgent need to achieve equity in cancer treatments. The propos-

als for a network of Cancer Centres and Cancer Units set out in the report of the advisory group convened by the Chief Medical Officer, Dr (now Sir) Kenneth Calman; "A Policy Framework for Commissioning Cancer Services" would at least provide the infrastructure on which such a service could be achieved.

References:
1 CR Gillis, DJ Hole. Survival outcome of care by specialist surgeons in breast cancer: a study of 3786 patients in the west of Scotland. British Medical Journal 1996 312: 145-8.
2 CJ Todd, CJ Freeman, C Camelleri-Ferrante et al. Differences in mortality after fracture of the hip: the East Anglian audit. British Medical Journal 1995 310: 904-8.

COHORS, COHORTIS (F):
A TENTH OF A LEGION

Dimensions and definitions

A cohort study follows a group of people from one point in time to another and observes changes that occur . It can be retrospective, for example reviewing all cases of breast cancer , or prospective, identifying a group of patients and following them through time. Cohort studies use routine data or data specially collected for the study or both. This type of research is useful for studying:-

- The outcome of treatment where a randomised controlled trial is impossible, for example the outcome of intensive care. The findings of this type of study allow quality standards, for example the readmission rate, to be evidence based.

- Different approaches to service delivery and management where these cannot be tested by a randomised controlled trial either because the number of units are too small to give a trial of adequate power, or because the health service policy makers or managers will not allow their service to be included in such a trial. In addition, cohort studies are also useful means of studying "natural experiments" i.e. when changes are made in the organisation or delivery for political or managerial reasons, or where different patterns of care exist in similar settings as a result of history and tradition.

Cohort studies have been used to study:

- The effects of staffing changes, for example the effect of introducing on-site physician staffing to intensive care units in hospitals other than teaching centres.
- The relationship between volume and quality
- The relationship between status and organisation of the hospital and outcome; whether or not it is a teaching or non-teaching hospital or whether the hospital is public or private.
- The relationship between the organisation of a clinical service and clinical outcomes.
- The relationship between different levels of qualification and outcome.

The balance between direct experimentation, though trials, and observational studies (such as the previous article on breast cancer in Scotland) has to be continually reviewed.

It is possible to organise randomised controlled trials to assess the benefits of different types of service or even the method of health care financing. However, for many questions about the relationship between the funding and organisation of care and patient outcomes, well conducted cohort study is an appropriate form of research design provided that the study is carefully appraised.

Questions to ask about a cohort study

These are the questions to ask. Answers for the West of Scotland breast cancer study are given after each question:

Q: Is clear information given about the way in which the cohort was recruited?

Very clear - all identified patients, using histological definitions

Q: Were any factors that could have included or excluded more severe cases considered?

No - about 98% of identified patients were traced and their history recorded.

Q: If mortality is an outcome, what steps have been taken to ensure that all deaths have been identified?

Through extensive searching of hospital records and death registrations.

Q: If other measures are used, have the instruments used for measurement been validated?

Does not apply

Q: Was the severity of disease taken into account in the analysis?

Yes: confounding issues like severity of breast cancer were analysed for . This made the result more positive.

Q: Was the presence of other diseases (co-morbidity) taken into account in the analysis?

No. May not apply

Features to note

When appraising a cohort study the most important feature is the completeness of recruitment. All the subjects in a defined time period should be recruited.You should suspect bias if there is any deviation from this, such as recruiting only patients admitted on weekdays, or between 0900 and 1700 hours. Check where patients went who were not admitted. Did the hospital refer more difficult cases elsewhere or does the referring doctor send only mild cases to that hospital?

Secondly ensure that valid criteria were used. Inpatient mortality is an invalid criterion of the quality of the hospital care because of variations in duration of stay. It is better to use thirty day or sixty day mortalityWhen criteria other than mortality

are used, such as pain or quality of life, the tools used should be validated measuring instruments.

Finally the analysis must take the severity of illness into account and explicitly record this. In studies of intensive care for example, a validated system for assessing severity - the APACHE (Acute Physiology and Chronic Health Evaluation) system is used. It is also essential to take into account the presence or absence of other diseases which might have influenced outcome, what is called the co-morbidity Robust techniques have been developed for doing this and must be used if valid results are to be obtained.

This problem was highlighted in ***Bandolier*** 23 (page 3). Patients whose appendix was removed at the same time as their gallbladder appeared less likely to die - this result was wrong because co-morbidity was not eliminated. The 'true' result was that taking out the appendix led to significant increase in nonfatal complications.

Uses and Abuses

The main abuse of a cohort study is as a means of assessing the effectiveness of a particular intervention when the more appropriate method could be a randomised controlled trial. Cohort studies are appropriate when assessing changes in service management or organisation, and in searching for rare unwanted effects of treatment.

UNLOCKING KEYHOLE SURGERY

Randomised controlled trials of surgical interventions are not common. Laparoscopic techniques are fashionable, and in some situations are now used widely. Repair of inguinal hernia is frequently carried out as a day-case procedure, so advantages of laparoscopic techniques are less likely to be apparent. Even so, results from well conducted RCTs examining a number of outcomes are welcome.

Design

A recent study [1] randomised patients having day-case hernia repairs to open or laparoscopic surgery (with full details of the type of procedure detailed in the original article). Surgery was performed by four surgeons who were experienced laparoscopists, and the operations were carried out under general anaesthesia.

Patients were given supplies of analgesic tablets (diclofenac, co-proxamol and pethidine) for different degrees of discomfort and were told that they could return to work or normal activity as soon as they wished. Questionnaires were administered to the patients for the first 10 postoperative days, and at six weeks.

Outcome measures

The principal outcome was the rate of short-term complications - an accidental event or secondary disease process resulting from the operation and occurring within 6 weeks. Other outcomes were daily pain scores, a profile of health status, time to return to work, and resource consumption.

Results

Complications occurred more frequently (7/58 patients) with laparoscopy compared with open operations (1/66). The number needed to treat with laparoscopic techniques to produce one extra complication was 9 (95%CI 5 - 60).

Laparoscopic surgery produced less pain in the days after surgery both on movement and on coughing, but not at rest. There was also a significant trend to lower tablet consumption with laparoscopic surgery but using tablet consumption of more or less than 10 tablets as a surrogate for overall pain, there was no significant difference - 34/55 taking fewer than 10 tablets after laparoscopic surgery compared with 38/66 after open surgery, odds ratio 1.0 (95%CI 0.5 - 2.2). The median time to return to work was 22 days after laparoscopic repair, compared with 28 days after open repair.

Laparoscopic repair was the more expensive option. This operation had an average cost of £850 compared with £268 for open repair.

Comment

This well conducted study from the Health Services Research Unit and Department of Surgery at Oxford showed that on current evidence laparoscopic procedures for hernia repair are associated with more short term risks and higher cost, with some marginal benefits in postoperative pain.The authors conclusion is that results of larger trials of different surgical techniques should be known before this technology is widely adopted.

Reference:

1 K Lawrence, D McWhinnie, A Goodwin et al. Randomised controlled trial of laparoscopic versus open repair of inguinal hernia: early results. British Medical Journal 1995 31 1: 981-5.

Immunotherapy for allergic conditions is one of those topics about which people seem to be wholly unmoved, or passionate believers. There may be circumstances where it is important - for insect sting reactions, perhaps - or in hay fever caused by airborne allergens.

For bronchial asthma it is a controversial topic. "What is the evidence that there is any benefit?" is the obvious question. What we decide to do with that evidence is the one that follows hot in its tracks. ***Bandolier*** certainly can't help with the second of these, but it can point to a meta-analysis of randomised studies which is likely to be of interest to those involved in trying to answer it.

Meta-analysis

The meta-analysis [1] was done by a group in Melbourne. They identified 20 randomised, placebo-controlled double-blind trials of immunotherapy for asthma between 1966 to 1990; English language reports only were used.

Data extracted

They looked at age of patients, allergen preparations used, adverse effects, and primary outcome measures like symptoms, medication, lung function and bronchial hyperreactivity (BHR). Data for house dust mites and other allergens (animal epithelium, mould or pollen) were presented separately The results are given in terms of odds ratios, but the meta-analysis contains no information that would allow the calculation of numbers-needed-to-treat.

Results

The results for symptom control, for reduction in medication and for BHR were all positive, as shown in the table with 95% confidence intervals. The effect of mite immunotherapy on lung function just achieved statistical significance, but was of little clinical significance.

There were many reports of local reactions at the injection site with allergens, with systemic reactions occurring in 32% (95%CI 20 - 44%). There were four reports of anaphylaxis. With placebo injections, systemic adverse effects occurred in 18% (95%CI 7 - 29%) of patients. There were no reports of anaphylaxis following placebo.

So what is the answer?

The authors calculated that 33 negative unpublished trials would be needed to reverse the conclusions of their meta-analysis. Their conclusion was that there is a solid basis to consider this treatment effective.

They also spend some time examining evidence about serious adverse effects like anaphylaxis. They report several surveys which examine this rare but life threatening event:

- 31 of 14, 639 mite or pollen injections - a rate of 1 in 500.
- 19 deaths in the USA in the five years till 1991 due to allergen immunotherapy 16 of which were in asthmatics - with no denominator but with unstable asthma or overdose of allergen as a major precipitating factor as the main contributors.

Their conclusion, that allergen immunosuppression *may* be a useful adjunct to therapy in allergic asthma was followed by many caveats:-

- an identifiable allergen
- full assessment of risks and contraindications
- initial consultant assessment
- close consultant supervision
- specific and effective allergen extract
- structured follow-up
- flexible dosing regimen
- facilities and staff to allow for treatment of adverse effects
- more trials - large, multicentre, randomised, with different outcomes

Results of immunotherapy using house dust mite or other allergens (odds ratios & 95% confidence intervals)

Outcome	House dust mite [number of patients]	Other allergens [number of patients]
Symptoms	2.7 (1.7 - 4.4) [286]	4.8 (2.3 - 10.1) [140]
Medication reduction	4.2 (2.2 - 7.9) [252]	no results
Bronchial hyperreactivity	13.7 (3.8 - 50) [95]	5.5 (2.8 - 10.7) [178]

All in all, not the most enthusiastic of recommendations. But this is just an extreme case of weighing up the benefits and harms of an intervention. It would be nice to have a simple answer, but they are not always available, and ***Bandolier*** certainly doesn't have a view here.

Reference:-

1 MJ Abramson, RM Puy, JM Weiner. Is allergen immunotherapy effective in asthma: a meta-analysis of randomized controlled trials.American Journal of Respiratory Critical Care Medicine 1995 151; 969-74.

So what is a QALY?

Bandolier has been perplexed at the concept of QALY - a slightly mythical creature of dubious parentage, but one which can sometimes dominate discussion of health topics. We were delighted, therefore, to have the topic explained simply by Ceri Phillips, a health economist from Gwent. His "simple" guide to QALYs follows.

Outcomes

Outcomes from treatments and other health-influencing activities have two basic components - the quantity and quality of life. Life expectancy is a traditional measure with few problems of comparison - people are either alive or not.

Attempts to measure and value quality of life is a more recent innovation, with a number of approaches being used. Particular effort has gone into researching ways in which an overall health index might be constructed to locate a specific health state on a continuum between, for example, 0 (= death) and 1 (= perfect health). Obviously the portrayal of health like this is far from ideal, since, for example, the definition of perfect health is highly subjective and it has been argued that some health states are worse than death.

Uses

Construction of such measures has a number of uses - to identify public health trends for strategies to be developed, to assess the effectiveness and efficiency of health care interventions, or to determine the state of health in communities.

QALY calculation

The Quality Adjusted LifeYear (QALY) has been created to combine the quantity and quality of life. The basic idea of a QALY is straightforward. It takes one year of perfect health-life expectancy to be worth 1, but regards one year of less than perfect life expectancy as less than 1. Thus an intervention which results in a patient living for an additional four years rather than dying within one year, but where quality of life fell from 1 to 0.6 on the continuum will generate:-

4 years extra life @ 0.6 quality of life values	2.4
less 1 year @ reduced quality (1 - 0.6)	0.4
QALYs generated by the intervention	2.0

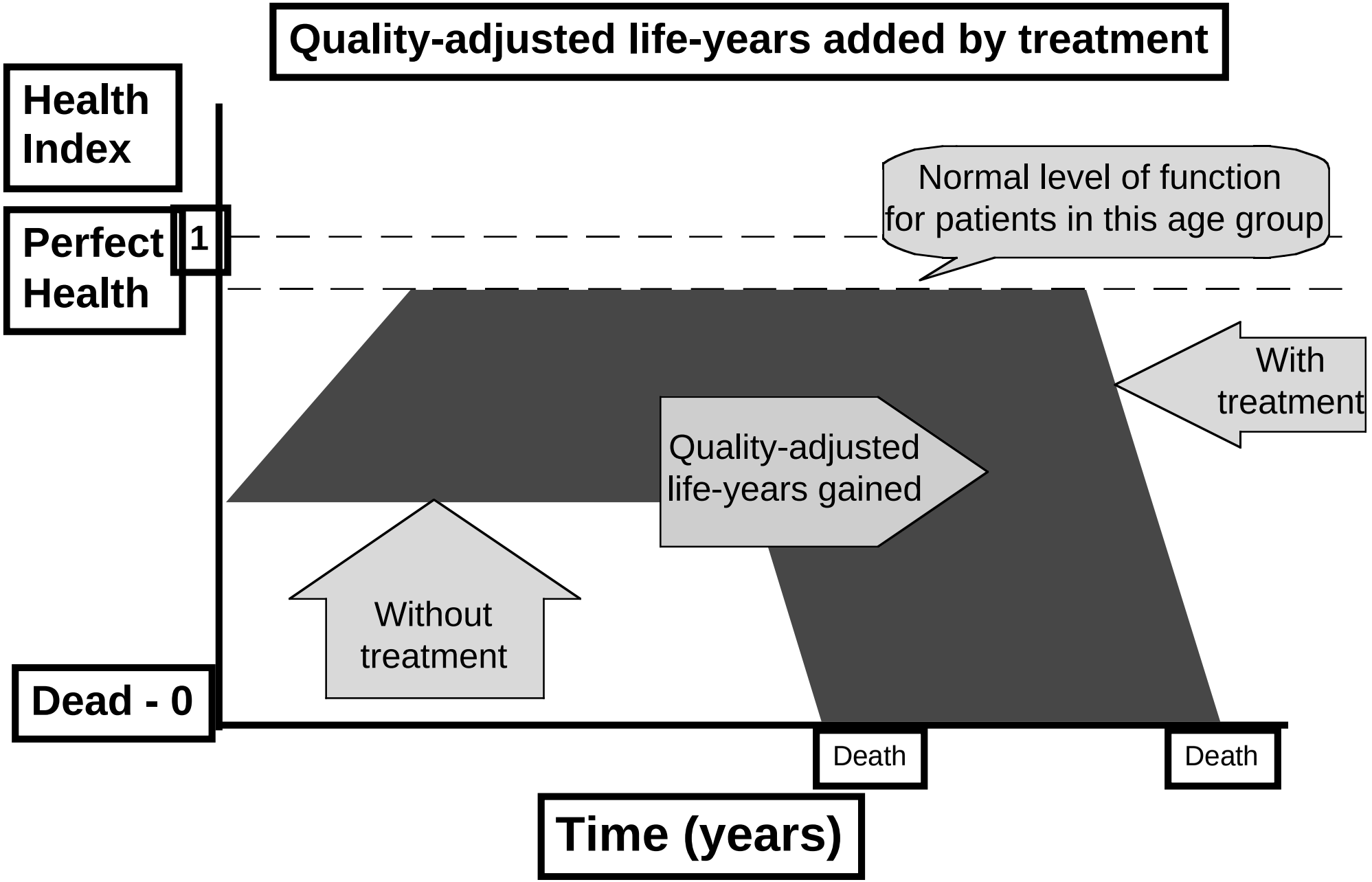
QALYs can therefore provide an indication of the benefits gained from a variety of medical procedures in terms of quality and life and survival for the patientAnother example is shown in the graph, where treatment provides a higher area under the QALY/time curve than does no treatment.

Value of QALYs

It is no use pretending that QALYs are anything but a crude measurement. It is necessary to be aware of their limitations - with the possibility of more research making the process more sophisticated and useful.

The use of QALYs in resource allocation decisions does mean that choices between patient groups competing for medical care are made explicit. QALYs have been criticised because there is an implication that some patients will be refused or not offered treatment for the sake of other patients and, yet such choices have been made and are being made all the time. However big the pot, choices still have to be made.

Dr Ceri Phillips Newport


Quality-adjusted life-years added by treatment
Health Index
Perfect Health
1
Normal level of function for patients in this age group
With treatment
Quality-adjusted life-years gained
Without treatment
Dead - 0
Death
Death
Time (years)